REMARKS

This paper is submitted in response to the Office Action mailed September 10, 2002. Claims 53, 57, 65 and 68 have been amended. Claims 72-80 have been added. No new matter has been introduced as a result of the amendments and submission of new claims. Support for the amendments to the claims is found in the specification, claims and attached Declaration. Attached hereto is a page captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE" indicating the changes made to the claims.

The Rejections Under 35 U.S.C. § 112, ¶ 2 Should Be Withdrawn

The Examiner has rejected claims 65-70 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that it is unclear what "extract" is claimed by the composition claims. In particular, the Examiner refers to samples collected from the fractionation steps that could also constitute "extracts." The Examiner also alleges that the claimed product, which is presumed to be different from the prior art, is prepared by the identical process. Furthermore, the Examiner has requested that the claims be amended to recite the steps in the method to define the composition claims.

Applicant has amended claim 65 to recite the steps utilized to prepare the claimed composition. Support for the amendment can be found at page 17, lines 14-16, of the specification. Applicant asserts that amended claim 65 clearly recite the steps in the method used to obtain the claimed composition comprising an extract from *Aristolochia taliscana*. It defines the extract as being obtained from the extraction step and not from subsequent fractionation steps disclosed at page 17, lines 16-29.

Claim 65 has been amended to recite steps in the process used to prepare the extract, as suggested by the Examiner. As amended, claim 65 clearly and distinctly claims the subject matter of the invention, and as a result defines the "extract" of the claimed composition. Accordingly, the Applicant respectfully requests the withdrawal of the rejection of claims 65-70.

The Rejections Under 35 U.S.C. § 112, ¶ 1 Should Be Withdrawn

The Examiner has rejected claims 53, 57-60, and 63-64 under 35 U.S.C. § 112, first paragraph, because the specification while enabling for a method for inhibiting plant fungal growth *in vitro* or inhibiting mutagenesis in a microorganism via administration of an organic solvent extract of *Aristolochia taliscana*, does not reasonably provide enablement for a method of inhibiting mutagenesis or fungal growth in any organism such as mammals. In particular, the Examiner alleges that the Applicant has only shown inhibition of *two* mutagens which are known mutagens to *one* bacterial species of microorganism and have not shown that the mutagens and bacterial species are considered representative of the countless mutagens and bacterial species which are known in the art. Because the biochemistry of mammals is different from that of bacterial cells, the Examiner concludes that she cannot extrapolate inhibition of mutagenesis of bacteria using the Ames test to inhibition of mutagenesis *in vivo* in mammals. The Examiner concedes that the Ames test may be a good indicator of potential mutagen *in vivo*, but contends that the test does not provide a direct correlation to what may be considered an inhibitor of a mutagen *in vivo*.

Applicant respectfully disagrees with the opinion of the Examiner. The Ames test is a widely accepted means of establishing mutagenicity of various compounds (Maron et al., 1983: Exhibit 1). Maron et al. recommends the use of Salmonella strain TA100, as shown in Example

2 of the present specification, for general mutagenicity testing and therefore supports the breadth of claim 53. Furthermore, the Ames test is used as a means to predict *in vivo* mutagenic/carcinogenic activity (See Maron et al., 1983, pp 174-175, Exhibit A). 80-95% of known carcinogens tested using the Ames test were shown to be mutagenic. Although candidate mutagens can produce "false positives" due to cytotoxicity in the Ames test (See Hayatsu et al., 1988, p. 430, Exhibit 2), a number of studies ***demonstrate a strong correlation between a positive Ames test result and in vivo carcinogenesis*** (Amonkar et al., 1989 (Exhibit 3); Anisimov et al. 2000 (Exhibit 4); Kaur et al. 2002 (Exhibit 5); Yamagishi et al., 2002 (Exhibit 6)). Each of these studies document that the observed anti-mutagenic effects of compounds using the Ames test could also be reflected in accepted *in vivo* models of tumorigenesis. For example, mutagenic effects of tobacco-related mutagens, NNN (nitrosonornicotine) and NNK ((4-nitrosomethylamino-1-(3-pyridyl)-1-butanone)) was inhibited by hydroxychavicol (HC) using the Ames test (Amonkar et al., 1989; Exhibit 3). Likewise, HC was also found to signficantly reduce the number of micronuclei induced by NNN and NNK using the *in vivo* assay in Swiss mice (Amonkar et al., 1989; Exhibit 3). Similarly, melatonin reduced the mutagenicity of DMBA (7, 12-dimethylbenz[a]anthracene), an inducer of mammary, cervival, and vaginal carcinogenesis) using the Ames test ***and*** an *in vivo* mouse model (Anisimov et al., 2000; Exhibit 4). Organic solvent extracts isolated from the bark of *Acacia auriculiformis* and *Acacia nilotica* demonstrated anti-carcinogenic activity against DMBA using the Ames test **and** also reduced the incidence of DMBA-induced lesions in a mouse mammary gland organ culture model (Kaur et al., 2002; Exhibit 5). Cacao liquor proanthocyanicidins (CLPr) derived from cocoa plants decreased the mutagenic effects of PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine) using the Ames test **and** reduced the incidence of PhIP-induced tumors in Sprague-Dawley rats

(Yamagishi et al., 2002; Exhibit 6). Thus, these references show that a positive Ames test can strongly support inhibition of mutagenesis/carcinogeneis *in vivo*.

In addition, the Examiner alleges that the instant specification discloses that the claimed composition comprising an extract from *Aristolochia taliscana* is inhibitory towards pathogenic plant fungi and lacks evidence that the claimed composition is inhibitory towards fungi that infect mammals. The Examiner contends that the lack of representative examples and art recognized unpredictability would require undue experimentation. The Applicant respectfully disagrees.

The plate diffusion method disclosed in Example 5 is a straightforward, widely accepted assay used to determine antifungal activity. Test compounds are spotted onto agar plates, seeded with a fungal species. Although the specification only discloses the use of plant fungus species as pointed out by the Examiner, it would be routine to substitute fungal species that infect mammals, such as *Candida albicans, Aspergillis fumigatus*, *Trichophyton mentagrophytes* and *Cryptoccocus neoformans,* and such substitutions would not require undue experimentation. Marchetti et al. demonstrates the activity of two candidate antifungal compounds, fluconazole and cyclosporine, against *Candida albicans,* using a plate diffusion assay (Marchetti et al., 2000; Exhibit 7). The assay for determining antifungal activity is simple and Applicant asserts that it is well within the knowledge of one of skill in the art to apply such a standard assay to various fungal species. Furthermore, the specification need not disclose what is well-known to those in the art and preferably omits that which is well-known to those skilled and already available to the public. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F2d 1367, 1384; 231 U.S.P.Q. 81, 94 (Fed Cir. 1986) *cert denied*, 480 U.S. 947 (1987). As a result, Applicant asserts that the specification discloses adequate support for enabling the presently claimed method of inhibiting

fungal growth in a substrate. Applicant respectfully requests the withdrawal of the rejection of claims 53, 57-60, and 63-64.

The Rejections Under 35 U.S.C. § 102(b) Rejections Should Be Withdrawn

The Examiner has rejected claims 65-70 under 35 U.S.C. §102 (b) as being anticipated by de la Parra *et al.* (US 4782077). The Examiner alleges that the claimed composition employs the same process steps as the cited art and concludes that the composition inherently anticipates the present invention. The Examiner has required that the claims be made amended in a product by process form.

For a claim to be anticipated by a reference, "there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v. Gannett, Inc.*, 927 F.2d 1565 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991). Moreover, a claim is anticipated and fails to meet the requirement of §102 only when a single prior art reference discloses each and every element of the claimed invention. *Lewmar Marine, Inc. v. Barient*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987), emphasis added.

The Applicant has amended claim 65, as suggested by the Examiner. Amended claim 65 recites the steps in the process for obtaining an organic solvent from the plant material of *Aristolochia taliscana.*

Specifically, claim 65 has been amended to incorporate an extraction step that is performed at room temperature. The extraction step disclosed in the cited art uses a Soxhlet extractor, which requires the input of heat to achieve extraction of desired compounds (see

Exhibit 8). Using a Soxhlet extractor, the sample material is placed in a extraction tube on top of a flask containing an organic solvent. The solvent is then heated, causing the vapor to travel into the extraction tube containing the sample material to extract the desired compounds from the material. The presently claimed composition comprises an extract that is isolated from an extraction method performed at room temperature and not a method that requires heat. Since the prior art does not disclose this element of the presently claimed invention, de la Parra *et al.* cannot anticipate the presently claimed invention. Therefore, Applicant respectfully requests the withdrawal of the rejection under 35 U.S.C. § 102(b).

New Inflammation Claims Are Supported by the Attached Declaration

Applicant has added new claims directed to the use of *Aristolochia* extracts for the treatment of chronic inflammatory disease. Applicant submits herewith the Declaration of Peter Hylands Under 37 C.F.R. § 1.132, showing the anti-inflammatory effects of various compounds isolable from *Aristolochia taliscana*. These compounds are capable of inhibiting the production of proinflammatory mediators, such as prostanglandin E_2 (PGE_2), thromboxane B2 (TXB_2), and leukotriene B4 (LTB_4). The data demonstrate the potential of eupomatenoid 1, eupomatenoid 7, eupomatenoid 8 and licarin A for therapeutic applications against chronic inflammatory disorders, such as inflammatory bowel disease, rheumatoid arthritis, synovitis and psoriasis. Thus, Applicant submits that new claims 78-79 are supported by the present specification and attached Declaration.

CONCLUSION

For all the foregoing reasons, Applicant respectfully requests allowance of the pending claims 53, 57, 59, 60, 63-70, and 72-80.

Applicants enclose the fee required for a Petition to Extend Time for three months pursuant to 37 C.F.R. § 1.17(a)(3). If any additional fee is due, or if any overpayment has been made, in connection with the filing of this response, the Commissioner is authorized to charge any such fee or credit any overpayment, to our Deposit Account No. 02-4377. Duplicate copies of this sheet are enclosed.

Respectfully submitted,

BAKER BOTTS, L.L.P.

By: Carmella L. Stephens

Rochelle K. Seide
Patent Office Reg. No. 32,300

Carmella L. Stephens
Patent Office Reg. No. 41,328

Attorneys for Applicants

30 Rockefeller Plaza
New York, NY 10112-4498

(212)408-2500

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claim 53, 57, 65 and 68 have been **amended** as follows:

53. (Twice amended) A method of inhibiting mutagenesis in an organism, which method comprises administering to the organism, an effective anti-mutagenic amount of an extract from *Aristolochia taliscana*, said extract having been prepared by a process which includes extracting plant material from *Aristolochia taliscana* with an organic solvent[, such that the extract is substantially free of aristolochic acids].

57. (Twice amended) A method of inhibiting fungal growth in a substrate, which method comprises administering to the substrate an effective anti-fungal amount of an extract from *Aristolochia taliscana*, said extract having been prepared by a process which includes extracting plant material from Aristolochia taliscana with an organic solvent[, such that the extract is substantially free of aristolochic acids].

65. (Twice amended) A composition comprising an extract from *Aristolochia taliscana*, wherein the extract has been prepared by [extraction of plant material from the Aristolochia species with an organic solvent and]

collecting *Aristolochia taliscana* plant material,

pulverizing the plant material,

suspending the plant material in organic solvent to produce a suspension,

extracting the suspension at room temperature to generate an extract,

wherein the extract contains at least 10% by weight of a eupomatenoid[, wherein the extract is substantially free of aristolochic acids].

68. (Twice amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an extract from Aristolochia taliscana wherein the extract has been prepared by extraction of plant material from the Aristolochia species with an organic solvent, wherein the extract contains at least 25% by weight of a phenolic eupomatenoid compound, at least 8% of Licarin-A and at least 8% by weight of a non-phenolic eupomatenoid compound[, and wherein the extract is substantially free of aristolochic acids].

The following new claims have been **added**.

72. (New) A method according to Claim 59 wherein the extract contains eupomatenoid-1.

73. (New) A method according to Claim 59 wherein the extract contains licarin-A.

74. (New) A method of inhibiting mutagenesis in an organism, which method comprises administering to the organism, an effective anti-mutagenic amount of a compound isolable from Aristolochia taliscana, wherein the compound is selected from the group consisting of eupomatenoid-7, licarin-A and eupomatenoid-1.

75. (New) A method of inhibiting fungal growth in a substrate, which method comprises administering to the substrate an effective anti-fungal amount of a compound isolable from Aristolochia taliscana, wherein the compound is selected from the group consisting of licarin-A, aristolactam C, dihydrocarinatidine, compound 34, and E-germacrene.

76. (New) The method of claim 75, wherein the compound is capable of inhibiting plant fungal species.

77. (New) The method of claim 76, wherein the plant fungal species is selected from the group consisting of *Botryis cinerea, Rhizoctonia solani, Saprolegnia asterophora*.

78. (New) A method of treating a chronic inflammatory disease in a subject, comprising administering to the subject an effective anti-inflammatory amount of an extract from Aristolochia taliscana, said extract having being prepared by a process which includes extracting plant material from Aristolochia taliscana with an organic solvent.

79. (New) A method of treating a chronic inflammatory disease in a subject, comprising administering to the subject an effective anti-flammatory amount of a compound isolable from Aristolochia taliscana, wherein said compound is selected from the group consisting of eupomatenoid-7, licarin-A, eupomatenoid-8 and eupomatenoid-1.

80. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound isolable from Aristolochia taliscana, wherein said compound is selected from the group consisting of eupomatenoid-7, licarin-A, eupomatenoid-8 and eupomatenoid-1.

CONCLUSION

For all the foregoing reasons, Applicant respectfully requests allowance of the pending claims 53, 57, 59, 60, 63-70, and 72-80.

Applicants enclose the fee required for a Petition to Extend Time for three months pursuant to 37 C.F.R. § 1.17(a)(3). If any additional fee is due, or if any overpayment has been made, in connection with the filing of this response, the Commissioner is authorized to charge any such fee or credit any overpayment, to our Deposit Account No. 02-4377. Duplicate copies of this sheet are enclosed.

Respectfully submitted,

BAKER BOTTS, L.L.P.

By: Carmella L. Stephens

Rochelle K. Seide
Patent Office Reg. No. 32,300

Carmella L. Stephens
Patent Office Reg. No. 41,328

Attorneys for Applicants

30 Rockefeller Plaza
New York, NY 10112-4498

(212)408-2500